REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the following remarks.

THE DRAWINGS

Applicants appreciate the Examiner's acceptance of the drawing as filed.

INFORMATION DISCLOSURE STATEMENTS

Applicants thank the Examiner for considering the four Information Disclosure Statements previously filed herein.

FILING DATES TO WHICH CLAIMS ARE ENTITLED

The Examiner has assessed the filing dates to which he believes the claims which he has examined are entitled. Thus, Claims 1-12, 56-66 and 82-98 have been assessed by the Examiner in regard to the earliest filing date to which he believes they are entitled.

Applicants have amended Claim 82 hereinabove so that step (i) is conducted at a temperature from about 45 to about 80°C rather than from about 40 to about 80°C as previously recited. This revised range is not only supported by the instant application (e.g., page 13, lines 21-25) but also by page 12, lines 20-23, of Provisional Appln. No. 60/541,247, filed February 4, 2004; moreover, step (ii) is disclosed at least on page 14, line 3 and in Example 2 of 60/541,247; step (iii) at least on page 14, line 6 and Example 2 of 60/541,247; and step (iv) at least on page 17, lines 25-27, page 18, lines 7-10 and Example 3 of 60/541,247. Claim 88 is supported at least by page 12, lines 20-22 of 60/541,247. Thus, applicants concur with the Examiner that the filing dates of Claims 1-11, 56-65, 84, 86 and 87 are the filing date of Application No. 60/541,247, filed February 4, 2004, but add that the filing dates of Claims 82 and 88 are also the February 4, 2004 filing date of Application No. 60/541,247.

Applicants concur with the Examiner's assessment that Claims 12, 66, 83, 85 and 89 are entitled to the effective filing date of the present application; however, as

a national phase application, this application and thus Claims 12, 66, 83, 85 and 89 are entitled to the international filing date of PCT/US04/09387, that is, March 26, 2004. The Examiner's reference to November 14, 2006 as the filing date for these claims is incorrect, that date simply being the date on which the requirements of the last of the 371(c)(1), (c)(2) and (c)(4) requirements were received by the USPTO. In the official Notice of Acceptance of Application under 35 U.S.C. 371 and 37 C.F.R. 1.495, it is clearly stated: "The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363)."

Despite the foregoing, it is not understood why the Examiner has found it necessary to assess the priority dates of the examined claims, as no art has been cited which would make it necessary to make such an assessment.

ELECTIONS/RESTRICTIONS

Applicants' election, with traverse, of the invention of Group I, Claims 1-12, 56-66 and 82-98 has been acknowledged and acted upon. Applicants continue to maintain that the amorphous nature of the various entities which make up the complex, that is the intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex which is formulated into a solid dosage form is not disclosed or suggested by Schultz et al. even when read in conjunction with WO 97/18839, as Schultz et al.'s melt extrusion product would not be inherently the same as applicants' Claim 1 product. Applicants' reasons for so stating are set forth in the discussion of the references herein below. Based on the discussion below, applicants submit that because the elected claims are in fact patentable over the art of record, there is indeed the unifying feature to all of the claims which applicants pointed to earlier. Therefore, the withdrawn claims should be rejoined and examined.

OBJECTIONS TO THE SPECIFICATION

The disclosure has been objected to because of the blanks identifying provisional application numbers on page 23. By the foregoing amendment,

applicants have deleted the entire sentence containing the blanks because the applications in question have been abandoned.

The disclosure has also been objected to because of a typographical error on page 22, line 12. Applicants have corrected the error by the foregoing amendment.

It is believed that these amendments overcome the objections to the specification.

CLAIM REJECTIONS - 35 U.S.C. § 112

Claims 2, 11 and 57 are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because of use of the term "saturated." Applicants submit that the claims are indeed clear and particularly point out and distinctly claim what applicants regard as their invention.

The Federal Circuit has made it very clear that definiteness of claim language must not be analyzed in a vacuum but rather (1) in light of applicants' specification, (2) in light of the prior art, and (3) in light of the manner in which the claims would be interpreted by one of ordinary skill in the relevant art. When analyzed in accord with Federal Circuit decisions, applicants' claims are definite. Applicants' claims are understandable and define what they regard as their invention; according to the C.C. P.A. decision *In re Kamal et al. (CCPA 1968) 158 USPQ 120*, such claims meet the requirements of the second paragraph of 35 U.S.C. § 112. In an effort to make these claims and others containing similar language even clearer, applicants have modified the language that refers to the saturated complexes to make it clear that it is the complex cladribine-cyclodextrin complexes which are saturated. Applicants have also modified the language of Claim 11; it would of course be apparent to the person of ordinary skill that applicants were referring to a point <u>on the curve</u> of the phase solubility diagram. The claims as amended have the same scope as prior to the amendment; these are not narrowing amendments but merely clarification of the subject matter to which the claims were previously directed.

The Examiner has noted that the term "saturated" is not defined in the claims, but applicants submit that it is the function of the specification, not the claims, to define terms. Applicants have certainly explained what they mean by saturated, not only by the disclosure at page 10, lines 1-13, but also by the disclosure at page 6,

line 20 to page 7, line 2; by the disclosure beginning at page 13, line 14 through page 14, line 16, which details the procedure used to develop the phase solubility curve; and by the disclosure at page 15, lines 5-29. Very specific information is given, not only as to time and temperature and subsequent filtration, on page 13, lines 21-26, but also in the discussion extending from page 16, line 1 to page 17, line 14. The phase solubility diagram and the discussion of the phase solubility diagram in Example 1 (and by reference, the complexation portion of Example 2) describe exactly how this phase solubility diagram/curve was generated. One of ordinary skill need only select a point on the phase solubility curve to identify the proportion of cladribine and cyclodextrin appropriate for the described saturated complexes for the conditions used in applicants' study. Alternatively, one of ordinary skill can repeat applicants' study to obtain the same curve, or can create his/her own phase solubility diagram for other conditions which he/she selects. The point is that applicants' work is reproducible, based on the teachings of their specification; selection of the same conditions as described will afford the same results; thus, the meaning of the claims which use the word "saturated" and which refer to the phase solubility diagram is clear to one of ordinary skill. As to the Examiner's complaint that no standard is given such as temperature, pressure or solvent, this is manifestly untrue for it is perfectly clear that the solvent disclosed in the specification is water and that the temperature and time are discussed with particularity in the specification, including the Examples, as already pointed out. Pressure is not mentioned because the work was carried out at atmospheric pressure, as would be understood by the skilled worker (who would know that pressure need be indicated only if it deviates from atmospheric pressure). Therefore, while there is no need to determine the amounts for each composition, at least when the cyclodextrin is hydroxypropyl-β-cyclodextrin or even hydroxypropyl-γ-cyclodextrin (page 17, lines 9-14) and the phase solubility curve provided by applicants can be used, it would be a very routine matter for one of ordinary skill to create such a curve for other amorphous cyclodextrins or to merely combine cladribine with the chosen cyclodextrin using the conditions specified by applicants and then remove excess cladribine. This is a simple procedure given all of applicants' teachings; it is not rocket science but rather is well within the skill in the art.

For at least the reasons set forth above, applicants submit that the 35 U.S.C. § 112, second paragraph, rejection is untenable and should be withdrawn.

CLAIM REJECTIONS - 35 U.S.C. § 102

Claims 1-15, 11, 56-60, 82-90 and 84-98 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Schultz et al. U.S. Patent No. 6,194,395, as evidenced by Baert et al. WO 97/18839.

Before discussing the cited references, applicants would like to discuss the amendments made to the claims hereinabove which make clearer what applicants regard as their invention. The Examiner is thanked for his very thorough review of the specification and the claim language, which has made it possible for applicants to see that some of their original language might have been open to misinterpretation while other language could be interpreted more broadly than they had intended. The amendments to Claims 2, 11 and 57 (as well as to withdrawn claims containing corresponding language) clarify that it is the entire complex cladribine-cyclodextrin complex which is saturated and that the point is located on the curve defining the saturated complexes as in the Figure. Applicants have also amended Claims 1 and 56 (and thus their dependent claims as well), as well as corresponding withdrawn claims, so that both Claims 1 and 56 now specify that the complex cladribine-cyclodextrin complex is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex. This of course excludes anything else from the complex. Claim 1, drawn to a pharmaceutical composition comprising the complex, has been further amended (as have the withdrawn claims containing corresponding language) to specify that the composition comprises no significant amount of free crystalline cladribine therein. This means that no significant amount of free cladribine can be detected considering the sensitivity of the analytical method; see Example 2, page 31, lines 3-13, where this language finds specific support. Applicants teach throughout this application that free crystalline cladribine which is not in the complex is excluded; see for example, page 13, lines 19-28; page 16, lines 1-12 and 13-28; page 20, line 28 to page 21, line 11; page 21, lines 24-29; Example 1, pages 26-28;

and Example 2, page 28, line 3 to page 29, line 26 and of course page 31, lines 3-13. As described, excess cladribine is typically removed from solutions of the complex by filtering it off after the complex complex has been formed in water; subsequent lyophilization of the filtered solution and minimal further processing affords the claimed solid oral dosage form. Therefore, the claim amendments clearly do not introduce new matter.

The Examiner states that Schultz et al. disclose a solid pharmaceutical oral dosage form comprising cladribine and cyclodextrin and applicants agree. However, the Examiner claims that Schultz et al.'s disclosure meets the limitations of instant Claims 1 and 56, which applicants regard as an unwarranted conclusion. Similarly, applicants find no evidence in Schultz et al. that the Schultz et al. solid product is substantially identical to a product-by-process meeting the limitations of instant Claims 82-90 and 94-96.

Schultz et al. disclose the use of either crystalline or amorphous cyclodextrins for their compositions, since some of those named by the patentees are known to be crystalline while others are known to be amorphous. Applicants' complexes and compositions utilize only amorphous cyclodextrins. Thus, many cyclodextrins disclosed by Schultz et al. would be inoperative in the present invention, as they would afford crystalline rather than amorphous products. In stating that the limitations of Claims 3-5 and 58-60 are met by Schultz et al., the Examiner is focusing only on the cyclodextrins in common; he does not address the basic differences between the Schultz et al. solid dosage form and applicants' products. Applicants will agree, however, that Schultz et al.'s preferred cyclodextrin is hydroxypropyl- β -cyclodextrin, which is a cyclodextrin also specified in many of applicants' claims. Again, applicants do not dispute that the excipients may be (but are not necessarily) the same, but this does not arrive at the products of instant Claims 3 and 58 or 97 or 98. As to the amounts of cladribine and cyclodextrin, Schultz et al. disclose weight ratios of from 1 to about 15 mg. of cladribine to about 100 to 500 mg. of a cyclodextrin; this can give a cladribine:cyclodextrin ratio of anywhere from 1:500 to 15:100, or from 1:500 to 1:6.67. If one took the lower limits of each in ratio to the upper limits of each, one would arrive at ratios from 1:100 to 15:500, or from 1:100 to 1:33.34. Most of the 1:500 to 1:6.67 ratio does not even

encompass applicants' ratio, while the 1:100 to 1:33.34 does not embrace it at all. Certainly no guidance in this respect is given by Schultz et al. Moreover, Claim 11 herein has been reworded to clarify that the point is on the curve, as described in the instant specification, and certainly this feature is not disclosed in any way by Schultz et al. Moreover, the instant claims no longer allow for the presence uncomplexed cladribine in either the composition or the complex.

The Examiner correctly states that the Schultz et al. patent incorporates by reference the method of making their solid oral dosage form by utilizing the melt-extrusion process of Baert et al. The Baert et al. process is carried out by mixing the cyclodextrin and the active ingredient, heating until melting one of the components, forcing the mixture through one or more nozzles, and cooling until the mixture solidifies (page 5, line 24-29). Milling may follow. The term "melting" is used broadly by Baert et al. and includes transition to a glass; in particular cases, one component melts and the other dissolves therein forming solid solutions (page 5, lines 8-12). The extruded material may contain amorphous material or a solid solution (page 7, line 35 to page 8, line 7). While amorphous products are of interest, those which are mainly a solid solution are preferred (page 8, lines 11-23). In Table 1, on page 30, several different mixtures of hydroxypropyl- β -cyclodextrin and selected drugs were subjected to the Baert et al. process. As noted on page 13, lines 5-6, in every case, the mixture using this cyclodextrin gave a solid solution. The Examiner will note from Table 1 that the temperatures used, regardless of the identity of the drug, went as high as 292°C., with the temperatures for the itraconazole/HPβCD mixtures reaching 279°C-280°C. According to *The Merck Index* (copy of excerpt enclosed), itraconazole melts at 166.2°C while HPβCD melts at 278°C according to *LookChem* (copy of excerpt also attached).

In addition to the teachings of Baert et al. noted above, applicants draw the Examiner's attention to three of Baert et al.'s teachings which are of particular importance here:

1. On page 4, lines 5-7, Baert et al state:

   > The compounds that are suitable to be used in this technique are compounds that show no appreciable decomposition at the temperatures needed to melt and extrude the mixture of said

one or more active ingredients with the cyclodextrin or cyclodextrins.

2. On page 6, lines 14-19, Baert et al. state:

> The possible formation of these solid solutions is one of the further advantages of the present invention. It will be appreciated by a person skilled in the art that mixing two or more solids, i.e., one or more cyclodextrins and the active ingredient or ingredients, and subsequently melting these solids together give rise to different products than when the said solids are first brought into contact with water or another solvent and then extruded.

3. While Baert et al. have general teachings regarding ratios of from 1:100 to 100:1, particularly 1:10 to 10:1, especially 1:5 to 5:1, 1:3 to 3:1, preferably 1:1, Table 1 therein uses ratios of active ingredient: HPβCD of 1:3 or 1:1. Table 2 utilizes 1:1 ratios.

The only solid dosage form envisioned by Schultz et al. is a melt-extrusion product of cladribine and cyclodextrin prepared according to Baert et al. There is no evidence that such a product was ever prepared. Indeed, cladribine melts at 220-235°C with decomposition; see the enclosed excerpt from *Linscott's Directory* (copy attached) as well as that from *The Merck Index* (also enclosed). Thus, cladribine decomposes well below the 278°C melting point of HPβCD and well below the temperature used by Baert et al. for their melt extrusion; cladribine is therefore not suitable for the Baert et al. process, according to Baert et al.'s teaching that suitable compounds show no appreciable decomposition at the temperature they use (point 1 above).

Furthermore, Baert et al.'s teaching on page 6 that their melt-extrusion process affords different products than when their solids are first brought into contact with water (point 2 above) militates against the Examiner's finding that a cladribine/cyclodextrin product prepared by Baert et al.'s process is the same as applicants' product, which is, in fact, prepared by first contacting cyclodextrin with water. Indeed, it is the use of water that enables the formation of cyclodextrin-drug complexes; it is by complex formation that the water solubility of many drugs has

been previously improved. There is no teaching by Baert et al. that would lead one of ordinary skill to conclude that Baert et al made solid complexes; indeed, Baert et al. specifically teach on page 6 that their products are different from products obtained by first dissolving cyclodextrin and drug in water. Thus, a melt-extrusion product of cladribine and cyclodextrin cannot anticipate applicants' product which comprises a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein. Applicants' product is prepared by preparing the complex in water; Baert et al. teach they obtain a different product than one that can be obtained from water; moreover, applicants' process uses temperatures up to only about 80°C, far below the decomposition temperature for cladribine and far below the temperatures used by Baert et al. See Claims 82-89 herein.

Further, for an anticipation to be inherent, the reference must always provide applicants' product. There is no reason to assume that Schultz et al's solid product ever is the same as applicants'; indeed, Baert et al. clearly teach that it is different.

For at least the reasons set forth above, the anticipation rejection of Claims 1-5, 11, 56-60, 82-90 and 94-98 based on Schultz et al. as evidenced by Baert et al. is untenable and should be withdrawn.

CLAIM REJECTIONS - 35 U.S.C.§ 103

Claims 1, 6-10, 12, 56, 61-66, 82 and 91-93 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schultz et al. in view of Baert et al. We respectfully disagree.

Both Schultz et al. and Baert et al. are fully discussed above. In referring to the ratios disclosed by Schultz et al. for their melt extrusion solid dosage form, the Examiner has chosen to ignore the 1 mg. dosage at which the amount of cladribine begins; therefore, the range disclosed by Schultz et al. for cladribine:cyclodextrin varies from about 1:500 to 1:6.67. This is not even in accord with Baert et al.'s ratio of from about 1:1 to about 1:3. And if one uses Schultz et al's ratios proportionately,

low:low and high:high, one arrives at from 1:100 to 15:500 (1:33.34). In the former case, there is absolutely nothing in Schultz et al. that would lead to a specific ratio of from about 1:10 to about 1:16 or about 1:11 or about 1:14; it is applicants' own teachings which lead to these ratios. Likewise, the features of the other claims rejected under 35 U.S.C. § 103 are not disclosed by Schultz et al. Certainly Baert et al doesn't teach these ratios and if one looks at Schultz et al.'s suggested amounts proportionately, applicants' ratios are not even broadly encompassed by the reference. Still further, as noted earlier, Baert et al. clearly teach that the drug-cyclodextrin solid products of their melt extrusion process are distinctly different from products prepared in water; since applicants' products are prepared in water, they cannot possibly be the same as those obtained by the Baert et al. process incorporated by reference by Schultz et al.

Baert et al.'s ratios of active ingredient have been interpreted as mole ratios by the Examiner. There is no good reason for such an interpretation. The Examiner reasons that the fact that the active ingredients have different molecular weights leads to this interpretation, yet there are cyclodextrins of different molecular weights contemplated by Schultz et al. and by the present inventors and the ratios of Schultz et al. are clearly by weight (col. 6, lines 23-31), just as applicants' ratios are clearly weight ratios, e.g., Claim 8. Absent a teaching to the contrary, one of ordinary skill would assume that the ratios of Baert et al. are also weight ratios. At any rate, the Baert et al. melt-extrusion product is not one obtained by complexation in water; Baert et al. teach their melt-extrusion product is different from a product whose preparation begins by dissolving the drug and cyclodextrin in water. Therefore, any product that Schultz et al. might produce from cladribine and cyclodextrin subjected to Baert et al.'s melt extrusion product cannot be the same as applicants' complex cladribine-cyclodextrin complex which must be obtained from an aqueous solution which is treated in a specific manner. Baert et al. never suggests that they obtain a complex by their melt-extrusion process, much less one meeting the requirements of applicants' claims. Indeed, Baert et al. emphasize that their process, which is different, affords a different product than that obtained by first dissolving the drug and cyclodextrin. Likewise, applicants emphasize that applicants' process is strikingly different from Baert et al.'s process and thus logically would not afford the

product which Schultz et al. would be expected to obtain by subjecting cladribine and cyclodextrin to Baert et al.'s process. Moreover, applicants have formed a very special complex which contains a large amount of cladribine as an amorphous inclusion complex and as amorphous free cladribine associated with the cyclodextrin as a non-inclusion complex. Note too that the free cladribine associated with the non-inclusion product is amorphous, in contrast to the cladribine starting material, which is crystalline. Note also that applicants produce their product by first complexing in water at temperatures of from about 45°C to about 80°C, far below the temperatures used by Baert et al. Cladribine actually decomposes at temperatures below that used by Baert et al.

It is clear from the foregoing that a molecular inclusion complexation process, let alone the particular inclusion process utilized by applicants to form their unique complex cladribine-cyclodextrin complex, is not inherent in Baert et al.'s melt extrusion process and that Baert et al.'s process gives a different product. To hold otherwise would be to ignore Baert et al.'s own teachings.

In view of the foregoing, it is submitted that the present application is free of all record rejections and objections. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

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Attachments:

"Cladribine", *The Merck Index,* (2001), pp. 407-408, Thirteenth Edition, Merck & Co., Inc., Whitehouse Station, NJ

"Itraconazole", *The Merck Index,* (2001), p. 938, Thirteen Edition, Merck & Co., Inc. Whitehouse Station, NJ

"Hydroxypropyl-beta-cyclodextrin, CAS No. 94035-02-6" *LookChem*, http://www.lookchem.com/cas-940/94035-02-6.html, September 23, 2008

"Non-antibody Products (Kits, Proteins, Microbial Antigens, Tissues, Services, etc.) *Linscott's Directory of Immunological & Biological Reagents*, http://www.linscottsdirectory.com/browse/products/page:36, Records 1,751-1,800 of 130,353, September 11, 2008